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Peripheral nerve injuries: the recent surgical management strategies

Periferik sinir yaralanmaları: güncel cerrahi yönetim stratejileri

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ABSTRACT

Aim: Numerous individuals with peripheral nerve injuries (PNIs) have permanent disability, which is a major health concern. There are a number of potential causes of PNIs, including piercing injuries, compression, stretch, and ischemia. These injuries can present with a variety of clinical symptoms.

Materials and Methods: In order to clarify the many forms of injury, the peripheral nerve's anatomy is thoroughly explained in this review, which attempts to revisit key PNI ideas. In addition, the specific pathophysiological processes that follow a peripheral nerve damage and the related variables that might either support or undermine the body's ability to regenerate itself depending on PNIs classifications are also mentioned. Next, the recent therapeutic neurosurgical approaches that are accessible in cases of PNIs are described.

Results: Following our overview of the previous literatures on neurosurgical strategies for the management of PNIs, we can observe that surgical procedures are unfortunately very expensive and that their use has been limited due to a variety of adverse effects, such as immunosuppression, chromosomal abnormalities, and tumorigenicity.

Conclusion: In accordance with the source, location and extent of the injury, there are currently advantages to treating PNIs with both surgical and non-surgical approaches. These days, it is possible to identify innovative techniques with the aid of good information regarding incidences, existing practice, outcomes, and study types. Despite a great deal of research on this topic, full functional recovery is still a problem that has to be solved.

Keywords: Peripheral Nerve, Injuries, Surgical, Strategies

ÖZ

Amaç: *Periferik sinir yaralanmaları (PSY) yaşayan birçok birey kalıcı sakatlıklarla karşı karşıya kalmakta ve bu durum önemli bir sağlık sorunu oluşturmaktadır. PSY, delici yaralanmalar, sıkışma, gerilme ve iskemik gibi çeşitli nedenlerden kaynaklanabilir ve her biri farklı klinik semptomlarla ortaya çıkar. Bu derleme, periferik sinir anatomisinin ayrıntılı bir açıklamasını sunarak temel PSY kavramlarını yeniden gözden geçirmeyi amaçlamaktadır. Ayrıca, periferik sinir hasarını takip eden patofizyolojik süreçleri araştırmakta ve PSY sınıflandırmalarına dayalı olarak vücudun kendini yenileme kapasitesini destekleyen veya engelleyen faktörleri vurgulamaktadır. İncelemede ayrıca, PSY'lerin tedavisinde mevcut olan güncel terapötik nöroşirürji yaklaşımları da tanımlanmaktadır.*

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Gereç ve Yöntem: *Bu derleme, çeşitli yaralanma türlerini aydınlatmak amacıyla periferik sinirlerin anatomisini titizlikle tartışmaktadır. Periferik sinir yaralanmalarının tetiklediği spesifik patofizyolojik mekanizmalara dalmakta ve yenilenmeyi etkileyen ilgili faktörleri incelemektedir. Ayrıca, PSY'lerin ele alınmasında kullanılan güncel terapötik nöroşirürji stratejilerini de açıklamaktadır.*

Bulgular: *PSY'lerin yönetimi için nöroşirürji stratejilerine dair önceki literatürlerin gözden geçirilmesi, cerrahi prosedürlerin genellikle gerekli olmasına rağmen, çok pahalı olduğunu ve immün supresyon, kromozomal anormallikler ve tümör oluşumu gibi çeşitli yan etkiler nedeniyle kullanımının sınırlı kaldığını göstermektedir.*

Sonuç: *Yaralanmanın kaynağı, yeri ve kapsamı dikkate alındığında, PSY'lerin tedavisinde cerrahi ve cerrahi olmayan yaklaşımların her ikisi de avantaj sağlamaktadır. İnsidans, mevcut uygulamalar, sonuçlar ve araştırma türlerine ilişkin kapsamlı verilerle desteklenen alandaki gelişmeler, yenilikçi tedavi tekniklerine yol açmıştır. Bununla birlikte, tam fonksiyonel iyileşme sağlamak, geniş kapsamlı araştırma çabalarına rağmen hala önemli bir zorluk olarak kalmaktadır.*

Anahtar Sözcükler: *Periferik sinir, yaralanma, cerrahi, stratejiler.*

INTRODUCTION

PNI is known as damage or illness to the nerves that exit the central nervous system (CNS) to the body's remaining organs, while about 3% of trauma patients may exhibit PNIs (1,2). Throughout history, the majority of our understanding of peripheral nervous system (PNS) and PNIs has come from combat experiences (3). While caring for the wounded during World War II, Sir Herbert Seddon developed his PNI classification system in 1942 (4). However, in contemporary times, PNIs are frequently encountered in trauma situations unrelated to combat. These injuries have the ability to significantly alter a person's life and are frequently linked to high rates of morbidity, which raises the possibility of severe disabilities. These disabilities affect patients for the rest of their lives because they frequently manifest in young people who are working age (5).

Numerous factors, including trauma, compression, illness, or inflammation, can cause damage to peripheral nerves (6). According to etiological surveys, motor vehicle crashes (MVCs) account for the majority of PNIs (46%) and are followed by motorcycle crashes (9.9%) (7).On the other hand, explosions and shrapnel are the most frequent causes of PNIs during warfare (8). In general, gunshot wounds, falls, industrial accidents, stab wounds, vehicle versus pedestrian injuries, recreational motor vehicle collisions (e.g., snowmobiles), and assaults are other major causes of PNIs (7). Furthermore, 17.4% of surgically treated PNIs are iatrogenic injuries brought on by medical or surgical procedures, per one study (9).

PNIs can be blunt or sharp, transected or lacerated, depending on the form of injury; the nerves can also be shifted, stretched, contused, or even partially separated, resulting in neuromas or lesions in continuity (8,10). In the affected part of the body, these injuries may impair nerve function and result in symptoms like pain, weakness, numbness, or tingling. Depending on the location and extent of the damage, the symptoms will vary in intensity. It is important to note that because of their anatomical route, which places them superficially and in close proximity to a bone structure or joint, some nerves are more susceptible to damage and can be injured by compression or stretching. For instance, injury to the radial nerve (which runs down the humerus shaft's spiral groove) brought on by an incorrect extended sitting posture in a chair or “Saturday night palsy” (11). Clinically, this kind of damage manifests as weakness in the wrists and fingers. Other instances include injuries to the ulnar nerve and the common peroneal nerve in the lower extremities. Ulnar nerve damage following surgery is a common issue that accounted for up to 17% of cases in one cohort. It arises from a patient's malposition, which compresses or stretches the ulnar nerve at the elbow level (12). The common peroneal nerve might be compressed in the lithotomy position between the leg holder and the fibular head, especially in thin patients or during long procedures (13).

Depending on the circumstances, PNIs may require surgery, physical therapy, medication, or other treatments. The past few decades have seen improvements in peripheral nerve surgery outcomes due to the understanding of nerve

regeneration, advancements in microsurgical methods, and ongoing molecular biology research.

Anatomical Structure of Peripheral Nerve

Each peripheral nerve is made up of several longitudinal axon configurations known as "fascicles," which are encased in 3 layers of connective tissue. These layers include blood vessels that supply trophic support for the nerve fibres and sustain the fascicles (14–16). All of the fascicles that make up the peripheral nerve's outermost layer are called the epinerium, and the primary component of the epinerium is the areolar connective tissue, which permits nerve contraction and expansion (16). The inner part of the epinerium coats every fascicle and is filled with blood channels that moisten the nerve and some adipose tissue, while the exterior coating covering the entire nerve provides anatomical form and mechanical protection (15).

The perinerium, a thin, dense connective layer that encircles each fascicle separately, is the middle layer. Consequently, aids in preserving structural homeostasis and safeguarding the endoneurial environment (15,16). The endonerium, a thin layer of collagen fibres that envelops each axon inside the fascicle, is the final component of the inner layer. Although this layer is very elastic and has a narrow network of microvessels and capillaries, it provides minimal mechanical protection (15,16).

Every single myelinated axon has a close relationship with Schwann Cells (SC). Since these glial cells construct a fatty multi-layered membrane (many layers of SC membranes connected with secreted proteins) that isolates the axon, they are able to produce laminin-rich sheets of myelin. To improve the pace at which neural electrical impulses propagate along nerve fibres, myelin is crucial. The impulse travels in waves when the nerve fiber is demyelinated. However, conduction happens by a saltatory propagation in myelinated fibres. The increase in electric resistance along the cell membrane is another myelin function that contributes to a quicker impulse. SCs are the primary extrinsic mediators of peripheral nerve regeneration in addition to their function in the myelination process (16).

Pericytes, contractile cells linked to the endothelium lining of microvasculature that regulate blood flow and capillary dilatation, are another significant cell type found in the peripheral nerve environment. In the endoneurial microenvironment as well as the brain-nerve barrier, these cells support homeostasis (16,17). An outline of the anatomy of peripheral nerves is shown in Figure-**1**.

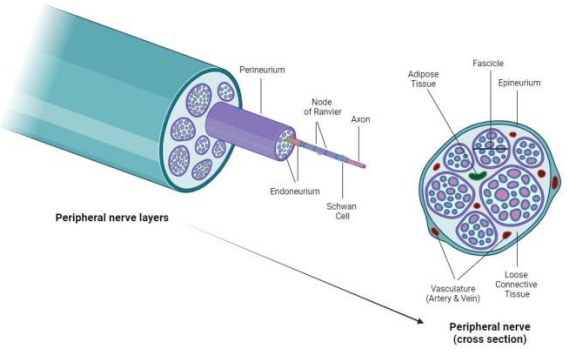

Figure-1. Diagrammatic illustration of a typical peripheral nerve (Created by using biorender.com and kleki.com).

Peripheral nerve injuries classification and implications

Experts have categorized PNIs into various classes based on their severity. This classification scheme facilitates the successful discussion of nerve pathophysiology and the choice of appropriate treatment by scientists and medical professionals (18).

1. Nerve injuries classified by Seddon

Sir Herbert Seddon developed what is known as Seddon's classification in 1943, dividing peripheral nerve injuries into three primary grades based on the degree of damage to the nerve's axons and connective tissue as well as the presence of demyelination. These consist of axonotmesis, neurotmesis, and neuropraxia (8). Table-**1** provides a succinct explanation of these injuries along with their effects.

2. Sunderland's nerve injury classification

In 1951, Sir Sydney Sunderland defined PNIs by further subdividing them into five grades based on the discontinuity of multiple layers of connective tissues. Table-2 summarizes the Seddon's and Sunderland's classifications.

Table-1. The classification of nerve damage by Seddon.

Neuropraxia	Axonotmesis	Neurotmesis
- This type of damage results in the partial or total loss of the nerve's ability to spread action potentials, while the vital axonal continuation is fully retained. Segmental demyelination of the nerve fibres is related to this condition. Although paralysis occurs, there is no peripheral deterioration (19). - The most vulnerable neurons are the motor neuronal fibres, which initially lose their ability to function and eventually regain it (20). - "Saturday night palsy" is an illustration of neuropraxia, where pressure builds up on a nerve while a person is asleep. On its own, this illness usually gets better in 12 weeks (21).	- Axonotmesis is the second grade of injury, characterised by extensive destruction to the nerve fibres that results in intact peripheral degeneration (22,23). In this kind of injury, the layers of connective tissue and the structures that are tightly connected to nerve fibres preserve the interior structures to an appropriate degree (24). - In this instance, neuropraxia is more worthy of the retrieval since it is good and spontaneous, yet Wallerian degeneration and axonal regrowth occur throughout (25). - Usually, no surgical intervention is required in this case (25).	- Neurotmesis, the third grade of nerve injury, damages the components of neural connective tissue and affects the perineurium, epineurium, and/or endoneurium. The nerve fibre is completely split into two ends, which results in total paralysis (26). - One unique characteristic of this damage is the Wallerian degeneration and axonal regrowth. This involves loss of the blood-brain barrier, axonal misdirection, and intraneural damage, all of which limit the healing process (25,27). - Surgery is now required for healing due to the injuries that resulted in damage to the perineurium and epineurium (25,27).

Table-2. The Seddon's and Sunderland's classifications of PNIs.

Seddon's Classification	**Neuropraxia**	**Axonotmesis**	**Axonotmesis**	**Axonotmesis**	**Neurotmesis**	
Sunderland's classification	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6 (According to MacKinnon)
Causes	Compression, traction, mild crush, and local ischemia	Nerve crush	Nerve crush	Nerve crush	Nerve transection and laceration	Closed traction damage, gunshot or stabbing wounds (28)
Pathophysiology	Nerve conduction block, continuity of connective tissues & axons	Axon division, but the connective tissue's layers are all still intact (29)	Endoneurial layer and myelin sheath are separated (30)	Axon with a detached perineurium, endoneurium, and myelin sheath (30)	Axon with detached endoneurium, perineurium, epineurium, and myelin sheath (31)	All grades engaged, mixed injuries (28)
Surgery	Not usually	Not usually (18)	Not usually	Usually necessary; protocol is dependent on the findings	Necessary; prompt nerve regeneration or repair (27)	Surgical exploration and intraoperative electrodiagnostic methods; nerve transplant or reconstruction (28)
Recuperation	Complete (Hours up to a few weeks)	Complete (Weeks to months) (18)	Incomplete and variable (Months)	Incomplete and variable, depending on injury and treatment (Months to Years)	Incomplete (Months to years)	Incomplete (Months to years)

Advances in treatment options and tactics for PNIs

Early nerve exploration and nerve restoration are two extrinsic factors that affect ho w long it takes for an injured nerve to heal. On the other hand, the rate of axonal regeneration can be as low as 1-2 mm/day, and there is no known medication that might quicken this process (32). After the muscle is denervated, the irreversible motor unit degeneration begins 12 to 18 months later and can last up to 26 months (33). Figure-2 illustrates potential surgical and non-surgical strategies for treating PNIs.

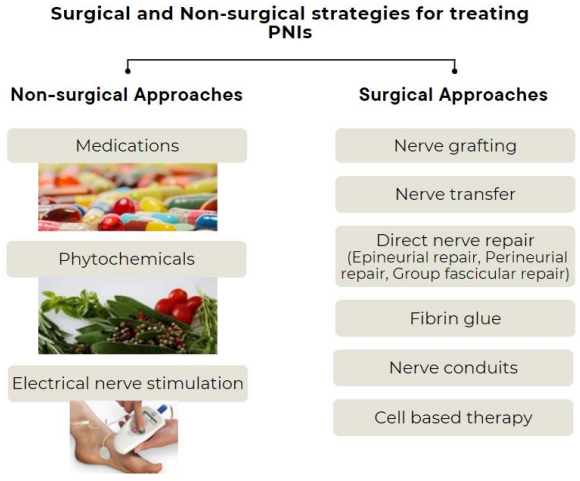

Figure-2. Potential surgical and non-surgical strategies for treating PNIs. (Created by using MS powerpoint).

Surgical treatment methods to restore peripheral nerve function

Following a PNI, there are six main neurosurgical categories of therapy treatments utilized to help facilitate the recovery of motor and sensory function.

1. Nerve grafting

Nerve grafting is a process whereby nerves from the same species are transplanted to fill up nerve gaps larger than 2 cm. By using this procedure, the fascicles' connective tissue should be severed rather than just one fascicle, and the gap be cut longer than the lesion. In respect to the lesion within normal tissue, the fascicles should be dissected at both the proximal and distal ends (34). The diameter of the host and donor nerves, the length of the nerve grafts, the number of fascicles, the pattern of fascicles, the cross-sectional area and form, and the patient's preferences are some of the criteria that should be taken into account when choosing a nerve donor (35). Nerve autografts, also known as autologous nerve grafts, and nerve allografts are the two types of nerve grafting that will be discussed in Table-3.

2. Nerve transfer

Applications: This surgical technique is employed to treat nerve injuries that result from total loss of motor and sensory function (45). If there is a significant injury to the proximal nerves, this may be the only reconstructive option available. For middle- and high-level injuries, the reconstruction is best done using extended nerve grafts to transplant the distal motor nerve. This technique shortens the time and distance needed for regeneration and permits segmentation in the planes of uninjured and unscarred tissues (46). In addition, it involves surgically reestablishing and reorganizing auxiliary motor units in order to restore the functional loss and sensibility (34).

Advantages: Because the surgical location for the nerve transfer is away from the damage site and uses identifiable, healthy tissues rather than the crushed or scarred tissues present at the injury site, it can be regarded as superior to nerve grafting. It permits the nerve's reinnervation into the intended muscle while maintaining the anatomical and biomechanical integrity of the nerve (47).

Disadvantages: Following nerve transfer, clinical outcomes take several months to manifest and require specialized technical knowledge. The validity of this approach is limited by the availability of donors and is extremely costly (48). Transfer of nerves cannot be viewed as a conventional therapeutic approach given the drawbacks.

3. Direct nerve repair

The most effective treatment for axonotmesis and neurotmesis is direct nerve restoration using microsurgical techniques to provide endurance or continuity between the distal and proximal part of the nerves (49). Direct nerve repair with microsurgical procedures to give endurance or continuity between the distal and proximal part of the nerves is the most successful treatment for axonotmesis and neurotmesis (35). Three categories of nerve repair treatments are included in Table-4; group fascicular repair, perineurial repair, and epineural repair (50).

4. Fibrin glue

Applications: Fibrin glue works by employing fibrin sealants, a sticky substance, to facilitate

primary sutureless healing. It is regarded as a successful method of preventing suturing for nerve cooptation (55,59).

Benefits: Fibrin glue repair guarantees reduced fibrosis, fewer inflammatory reactions, and a quicker recovery period (60). The primary benefit of fibrin glue is in its rapid and effortless application for nerve repair in emergency situations when a skilled surgeon is not available (61). However, it is not suitable for serious damage. A perfect sealant should possess particular mechanical, structural, and biological characteristics and shouldn't impede the process of regeneration (55).

Drawbacks: The usage of human blood in commercially available sealants is their greatest drawback, since it can lead to the spread of infection, fibrosis, toxicity, and necrosis (62). This has led to the discovery of a novel heterologous fibrin sealant (HFS) produced from snake venom. It can stop fluid loss, shorten the duration of operation, and lessen bleeding (63).

5. Nerve conduits

Applications: Nerve conduits act as a link between the damaged nerve's proximal and distal stumps. They can be employed in place of nerve autografts and offer a scaffold for axonal regrowth. Recently, researchers have concentrated on creating conduits as a different kind of treatment, particularly for complicated abnormalities (52). By inserting distal and proximal stumps into both of the nerve conduit's ends, this approach enables axonal regeneration from the proximal stump through the conduit and selectively grows into the typical pathways in the distal nerve stump. Based on the materials they are made of, conduits are divided into two categories: synthetic conduits (more classified into non-degradable and degradable conduits) and biological conduits (64–66).

Table-3. Nerve grafts types; A) Nerve autografts, and B) Nerve allografts.

	A) Nerve autografts (Autologous grafts)	**B) Nerve allografts**
Applications	- The gold standard for peripheral nerve repair is autografts (36). - Autologous grafts improve recovery for more proximal injuries, severe nerve injuries, and lengthy nerve deficits (>3 cm) (37). - Donor nerve grafts are typically taken from expandable sensory nerves, such as the lateral and medial antebrachial nerves, the superficial sensory branch of the radial nerve, the dorsal cutaneous branch of the ulnar nerve, and the lateral femoral cutaneous nerve (38). - Different nerve autografts, such as cable, single, vascularized, interfascicular and single nerve autografts, have been employed, depending on the degree of the lesion (37).	- One of the best substitutes for nerve autografts is nerve allograft. For the purpose of nerve transplantation, allograft nerves are extracted from cadavers or donors (39). Allografts of cadaveric nerves are widely available and contain donor SCs and endoneural architecture, which promote regeneration (40). - Systemic immunosuppression is necessary in this procedure to prevent graft rejection, and the donor's stem cells serve as facultative antigens in addition to helping in remyelination. Furthermore, the systemic immunosuppression is transient and can be reversed if the host SCs have migrated sufficiently (around 24 months) (40,41).
Advantages	- Autologous grafts offer the best outcomes since it doesn't trigger an immune response and involves elements that promote neuron regeneration, such as Schwann cells, basal lamina, neurotrophic factors, and adhesion molecules (42).	- It avoids the morbidity of the donor site, is easily accessible, and comes in an endless supply (20).
Disadvantages	- Although autologous nerve grafts have been shown to produce positive outcomes, there are certain drawbacks to this procedure, such as restricted tissue availability, graft-related complications, donor-site morbidity, nerve function loss, scarring, the need for a second incision, formation of neuromas, limited supply, and possible differences in tissue size (42).	- The recovery results are good even though the treatment is too expensive and requires expertise to perform (43,44). - Tumor development and opportunistic infections are two of the several negative outcomes of immunosuppression (20).

Table-4. The three categories of direct nerve repair treatments.

	A) Epineural repair	B) Perineurial repair	C) Group fascicular repair
Applications	This method of repairing damaged nerves includes merely sewing the outer sheath of the injured nerve and can be applied to primary as well as secondary neural repairs (51).	- Hashimoto and Langley originally published a description of this method in 1917 (52). - Because it is a simpler and speedier approach that also entails just a little disruption of the nerve's internal structure, it is a superior option for suturing the epineurium and for large acute nerve lacerations (53).	When a nerve is lacerated and the branches of transected nerves are clearly arranged and identifiable inside the main trunk, this procedure is simple (34).
Advantages	- Its benefits include low magnification, speedy execution, avoidance of intra-neural contents, and ease of use (54). - The most crucial technique for achieving a tension-free natural connection with no loss of nerve tissue and exact alignment of the nerve fascicles is to perform nerve repair after nerve alignment (55).	After proper localization of fibers at nerve terminals, this nerve repair procedure has proven to be more beneficial in terms of calming and neural pathways, while also covering the neurophysiological and morphological elements of it (53).	Both the proper coordination of the motor and sensory fascicles and the avoidance of cross-innervation of motor sensory nerves are possible (34).
Disadvantages	None	Greater fibrosis at the nerve suture site, a lengthier surgical period, and discontinuities in fasciculi one-to-one are some of the disadvantages of this approach (56,57).	There are currently several drawbacks, such as a lengthy surgical procedure, which make it impractical (58).

Advantages: The conduits stop surrounding tissues from leaking into a gap between the stumps. Furthermore, axon regeneration after a nerve injury is facilitated by the abundance of neurotrophic substances in these conduits (53). The capacity of a conduit to create the perfect environment for neuronal repair is by far its greatest benefit. For this reason, the perfect nerve conduit should have the following characteristics: it should be thin, porous, biocompatible, permeable, flexible, biodegradable, compliant, and have the right surface for neuro-inductivity and neuro-conductivity (67, 68).

6. Cell-based treatment

The main drawbacks of current previous therapies are their inability to adequately fill in big gaps and their slow rate of nerve regeneration. In order to get around these restrictions, cell-based therapy was created to provide nourishing cells to the location of the lesion in an effort to hasten neuron regeneration, which could eventually take the place of all existing surgical treatments (69). Because stem cells may differentiate into specialized cell types and self-renew, they are used in cell-based therapy (70). SCs are the most researched therapeutic models, although other types of stem cells (Box-1) have also produced amazing results.

Box-1. Types of stem cells used in cell-based therapy for PNIs:

Schwann cells-mediated therapy

SCs are the most significant and preferred seed cells since they are the primary peripheral nervous system functional cells that promote myelination and regeneration (71). They are essential for nerve regeneration because they promote the manufacture of neurotrophic factors such as neuropeptide Y, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), platelet-derived growth factor, and neurotrophic factor (BDNF) (72). Moreover, SCs have the ability to migrate, remyelinate, modulate the immune system, and multiply themselves. The improvement of injured nerve regeneration and repair can be attributed to all of these variables. Neural crest cells are the primary source of SCs in cell-based therapy. The axonal regeneration process is accelerated by the transplantation of SCs seeds into nerve conduits. Regretfully, they are difficult to come by and have a sluggish proliferation to huge numbers (71).

Embryonic stem cells (ESCs)

The benefits of using ESCs are numerous and include the ability to produce an endless supply of cells, strong differentiation potential, and long-term proliferation capacity. However, the main issue with using these cells for transplantation is ethical issues (73).

Neural stem cells (NSCs)

NSCs have the ability to differentiate into neurons and glial cells; however, due to the difficulty in harvesting these cells and the possibility of neuroblastoma formation, their usage is restricted (74).

Bone marrow-derived stem cells (BMSCs)

The ability to develop into SC-like cells exists in BMSCs (BMSC-SCs). Studies have revealed that BMSCs' capacity for differentiation is weaker than that of NSCs (71).

Fetal stem cells (FSCs)

Fetal stem cells can be extracted from amniotic fluid, amniotic membrane, umbilical cord, and Wharton's jelly. Both umbilical cord-derived mesenchymal stem cells (UC-MSCs) and amniotic tissue-derived stem cells (ATDSCs) possess the ability to differentiate and proliferate. Two key advantages of fetal-derived stem cells are their low immunoreactivity and ease of acquisition. Regretfully, ethical issues are also fetal-derived stem cells' main disadvantage (75).

Adipose stem cells (ADSCs)

ADSCs have a high capacity for angiogenesis and increase the perfusion of injured neurons (76).

Dermal skin-derived precursor stem cells (SKP-SCs)

SKP-SCs can differentiate into any type of cell, including glial and neuronal cells, and are located in the dermis. They are said to quicken nerve regeneration (77).

Hair follicle stem cells (HFSCs)

One special quality of HFSCs is their ability to differentiate into SCs without the need for genetic modification. Studies on animals have shown that employing HFSCs can promote nerve healing (78).

Induced pluripotent stem cells (iPSCs)

The employment of substitute cells, such as iPSCs, has become necessary due to a number of disadvantages related to stem cells. Although they exhibit improved neural regeneration, their application has been constrained by their tumorigenicity, immunosuppressive need, and chromosomal abnormalities (79).

Conclusion and Future Directions

PNI is a well-known health problem that, depending on the degree of nerve damage, presents a wide range of signs and symptoms. There is a wealth of information on the pathogenic mechanisms of PNI and its regeneration, but there is still a dearth of trustworthy treatments that guarantee full and precise functional recovery. The process of recovery is extremely sluggish, and even with the use of numerous treatment techniques, full functional restoration remains unattainable. We have attempted to highlight the benefits and drawbacks of the current PNI neurosurgical treatments in this review. Currently, there are benefits to treating PNIs using both surgical and non-surgical methods. Regrettably, surgical techniques are highly costly, and their application has been restricted because of a number of side

effects, including immunosuppression, chromosomal abnormalities, and tumorigenicity.

Acellular human nerve allografts: Scientists are working on acellular human nerve allografts (ANAs) at the moment in an effort to get rid of immunosuppressants (41,80). The extracellular matrix (collagen, laminin, and growth factors) and internal neuronal structure are retained in ANAs that are extracted from SCs and myelin (81,82). The migrating SCs of the host are involved in the regeneration process with ANAs. Therefore, even if ANAs perform well in studies, they remain ineffective for lengthy nerve repairs (20,80). In the future, ANAs enhanced with growth factors and seed cells might enhance the results of surgical repair for a sizable gap in PNIs (20,83). Therefore, despite the wide range of applications and advancements in grafts, more advancements with improved prognoses are still required. Resolving the immunosuppression issue would be a significant advancement in this discipline.

Nerve sealants: It will be a significant advancement in this sector if more genuine and reasonably priced nerve sealants are found in the future to overcome the disadvantages of fibrin glue. Additionally, this endeavour might lessen the population that is afflicted with PNI.

Competing interest: The authors have no competing interest.

Abbreviations

PNIs	Peripheral nerve injuries
CNS	Central nervous system
PNS	Peripheral nervous system
SCs	Schwann cells
MVCs	Motor vehicle crashes
HFS	Heterologous fibrin sealant
NGF	Nerve growth factor
BDNF	Brain-derived neurotrophic factor
CNTF	Ciliary neurotrophic factor
FSCs	Foetal stem cells
ESCs	Embryonic stem cells
NSCs	Neural stem cells
BMSCs	Bone marrow-derived stem cells
BMSC-SCs	Bone marrow-derived stem cells Schwann cells-like
ATDSCs	Amniotic tissue-derived stem cells
UC-MSCs	Umbilical cord-derived mesenchymal stem cells
ADSCs	Adipose stem cells
SKP-SCs	Dermal skin-derived precursor stem cells
HFSCs	Hair follicle stem cells
iPSCs	Induced pluripotent stem cells
ANAs	Acellular nerve allografts

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